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PEOPLE & IDEAS

Bo Zhong: Captive by the viral immune escape

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Bo Zhong studies the regulation of the antiviral innate immunity, inflammation, and tumorigenesis by the protein ubiquitination system.

A scientific talk on HIV was the spark that ignited Bo Zhong's interest in immunology. Bo, a native of Hubei Province, China, openly confesses that he had little interest in his English major at the China University of Geosciences. It was 2002, and Dr. Xi'en Gui, a specialist in infectious diseases, reported on the AIDS epidemic that had stricken the Henan rural communities since the '90s. The words of Dr. Gui, and later the concepts discussed in the animal biology course imparted by Prof. Shiquian Huang, which Bo took, resonated in his mind. He found it fascinating how pathogens have evolved to survive within a host or in tough environments by evading the host immune system or outperforming their competitors, and the disruption of this balance with the undesired consequences of life-threatening diseases or bio-extinction was what really caught Bo's attention. With these questions bugging him, Bo enrolled in a minor in biological science and pursued a doctoral degree in life sciences under the supervision of Prof. Hong-Bing Shu at Wuhan University, China.

Bo's thesis was very productive—he published five first-authored papers, one of which described the identification and characterization of the central adaptor protein in innate antiviral immunity and autoimmunity, mediator of IRF3 activation (MITA)—also known as stimulator of interferon genes (STING; Zhong et al., 2008). His postdoctoral work was equally stellar—in 2010, amid the last throes of the 2008 financial crisis and deep cuts in science funding, Bo joined the lab of Prof. Chen Dong at the MD Anderson Cancer Center, Houston, TX, where he authored key contributions to the field of autoimmune disorders. He reported the first deubiquitinating enzyme, USP25, in regulating IL-17 signaling and IL-17–mediated autoimmunity (Zhong et al., 2012). Bo returned to China to establish his virology lab at Wuhan University in 2013, first as a faculty member of the College of Life Sciences and then as an adjunct professor at the Medical Research Institute. We contacted Bo to learn more about his current and future scientific endeavors.

Bo Zhong. Photo courtesy of Bo Zhong.

What drew your interest to the ubiquitin system and its function in the antiviral innate immune and inflammation responses?

The enzymatic activity of the deubiquitylation enzymes or the E3 ubiquitin ligases is required for their functions, and thus developing molecules to inhibit their activity could provide potential lead drugs to treat the related diseases. At the time I started my research group, the post-translational modifications of the cGAS-MITA/STING axis and T cell immunology were emerging, so I became interested in the ubiquitination-mediated regulation of the antiviral signaling and inflammatory responses. After recruiting a first batch of graduate students, I worked together with them to clone several E3 ubiquitin ligases and deubiquitinating enzymes, including USP25, and examined their roles in antiviral signaling and inflammation. After 2 yr of hard work, our efforts saw the light of the day, and our findings on the requirement of USP25 for the activation of type I interferons and proinflammatory cytokines in response to viral infection were published in PNAS (Lin et al., 2015)—that was my first publication as an independent principal investigator (PI). Since then, we have characterized the temporal and spatial ubiquitination and deubiquitylation of cGAS, MITA, and MAVS and their roles in innate antiviral immune responses.

What are you currently working on, and what is up next for you?

The proteins involved in antiviral responses also mediate self-nucleic acids–triggered inflammation, so I have extended my research interest to autoimmune disorders and inflammation-related tumorigenesis with an emphasis on ubiquitination and

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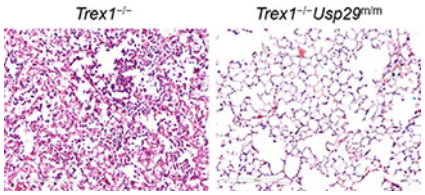

Images of lung sections of 5-wk-old *Trex1*$^{-/-}$ mice (left) and *Trex1*$^{-/-}$*Usp29*$^{m/m}$ mice (right). Knockout of USP29 rescues lung inflammation caused by Trex1 deficiency. Image courtesy of the Zhong lab.

The Zhong lab at the Medical Research Institute, Wuhan University. Photo courtesy of Bo Zhong.

secretory proteins. On one hand, we collaborate with clinicians to identify the ubiquitin-related proteins and secretory proteins that are associated with disease progression, relapse, prognosis, and drug resistance/responsiveness. By generating genetic mouse models, we try to examine the roles of the identified proteins in disease progression and elucidate the mechanisms. On the other hand, we are collaborating with the industry to develop small molecules or monoclonal antibodies to interfere with the activity or availability of the identified proteins. I hope these lead compounds or molecules can be used in the clinic for therapeutic intervention of the related diseases in the future.

What kind of approach do you bring to your work?

Well, I think the lab culture created by the starting lab members is very important for the success of a lab. In our lab, the graduate or PhD students have to be generous, helpful, and willing to share. I want to set the example my mentors, Hong-Bing and Chen, set for me, so I encourage and inspire my trainees and I care about their ideas. When they meet difficulties and approach me, I do my best to put aside whatever I'm doing at that moment and give them suggestions to overcome the shortcomings. That's what Hong-Bing did with me—no matter how busy he might be with administrative tasks, he always found time to sit with me to patiently teach me how to analyze and interpret the data and how to critically design the next-step experiments. It's also important to me to help my lab members achieve their goals—Chen always asked me what he could do to help me with my research and supported me through some risky projects so that I grew quickly as an independent researcher. So, at the end of the day, I do whatever it takes to keep my team enthusiastic and focused, even if sometimes that means playing cheerleader to fire them up.

I see your mentors have been fundamental to your way of approaching science and your lab. Is there anything you wish they would have better trained you in?

Probably grant writing—the funding support has always been and is currently challenging for almost every single lab, and a logical and clear proposal definitely multiplies your chances of success. I wish they would have trained me in how to efficiently operate a budget in COVID-19 times too [sighs]—import of the reagents and mice takes longer and is more expensive. Hope the pandemic will be over soon and everything goes back to normal.

Securing funding seems to have been your biggest challenge so far, but on a more positive note, what has been your biggest accomplishment(s)?

Scientifically, the identification of MITA/STING and its regulatory mechanisms in antiviral immunity and autoimmunity, but outside of the lab I have a 7-yr-old son and a 4-yr-old daughter, so, unquestionably, they are my biggest accomplishment in life.

Any advice you have been given for a successful research career?

To set up an ambitious goal and divide it into several small achievable goals and try your best at accomplishing the small goals every day, every month, and every year.

Finally, a little bit of wishful thinking… imagine that you rewind to day 1 of you being a PI; what would you change or repeat? What would you do research on if you had unlimited funding? And a more ambitious thought, if you could change or improve just one thing in academia, what would be?

These "if" questions are difficult to answer, but here I go. If I were to rewind to the first day of being a PI, I would be more confident and work harder. If I had unlimited funding, I would put more effort on the translational research to develop close-to-clinic small molecules and monoclonal antibodies for therapeutic interventions. And the third one… I hope that the Chinese government would invest more funding to basic research, as the increase of funding is far less than the increase of researchers.

References

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